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Prevalence of EBV RNA in sinonasal and Waldeyer's ring lymphomas

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A high incidence of a T cell phenotype of sinonasal lymphomas in other Asian countries has been associated with a high incidence of Epstein Barr virus (EBV) infection. We analyzed 13 sinonasal and 18 Waldeyer's ring lymphomas for the prevalence of EBV encoded RNA (EBER) using a sensitive and specific in situ hybridization. In addition, we examined the relationship of histologic findings and immunophenotype as well as the location of the lymphomas to the presence of EBV. The EBER was detected in each of 12 sinonasal lymphomas with a T cell immunophenotype. One B cell sinonasal lymphoma was EBER negative. Four of 18 Waldeyer's ring lymphomas were positive for EBER, including two T cell lymphomas. Two of 16 B cell Waldeyer's ring lymphomas were EBER positive. Morphologically, 11 of 20 diffuse large cell lymphomas, 2 diffuse mixed small and large cell lymphomas, 2 of 4 immunoblastic lymphomas and 1 lymphoplasmacytic lymphoma were EBER positive. Four follicular large cell lymphomas were EBER negative. A characteristic angiocentric or angiodestructive pattern was found in most T cell lymphomas and EBER positive cases. These findings indicate that EBV infection is more strongly associated with the T cell immunophenotype, angiocentric pattern and sinonasal location of the lymphoma.

Key Words : *EBV, sinonasal lymphoma, Waldeyer's ring lymphoma.*

INTRODUCTION

The Epstein Barr virus (EBV) is a B lymphotropic, polyclonal activator that stimulates cell division and immortalizes lymphocytes in vitro. The EBV related DNA, RNA or protein can be found in tissues involved by lymphoreticular malignancy including Burkitt's lymphoma (Epstin, 1964), post-transplantation lymphoma (Cleary et al., 1988), Hodgkin's disease (Weiss et al., 1987) and more recently T cell non-Hodgkin's lymphoma (Jones et al., 1988). For many years, it had been assumed that EBV only played a role in the pathogenesis of B cell lymphomas among malignant lymphomas. Recently it has been recognized that EBV may be associated with many types of T cell lymphomas. In large series of peripheral T cell lymphoma arising in the absence of overt immunodeficiency, the association with EBV was detected in 10% to 47% of the patients (Hamilton-Dutoit, 1992 ; Korbjuhn et al., 1993). In fact EBV positivity is more likely to be found in a T cell lymphoma than in a B cell lymphoma. Cases of EBV positive T cell lymphoma have associated with

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upper and lower respiratory tract lymphoma, particularly angiocentric lymphoma (Medeiros et al., 1992) and nasal lymphoma (Kanavaros et al., 1993; Arber et al., 1993), T cell lymphoma associated with hemophagocytosis (Gaffey et al., 1993) and angioimmunoblastic lymphadenopathy like T cell lymphoma (Weiss et al., 1992). Nasal lymphoma is the third most frequent group of extranodal lymphomas after gastrointestinal lymphomas and tonsillar lymphomas in Korea (Kim et al., 1992). Also, a high incidence of a T cell phenotype of nasal lymphoma has been described(Ko et al., 1992). Since the incidence of sinonasal lymphoma is high in Korea, similar to other Asian countries (Chan et al., 1987 ; Yamanaka et al., 1985) and a common environmental or ethnic influence is speculated, this study was designed to determine the prevalence of EBV in the 13 sinonasal lymphomas. In addition we examined the relationship of histologic findings and immunophenotype as well as the location of the lymphomas to the presence of EBV. Eighteen cases of Waldeyer's ring lymphomas were also studied for a comparative purpose.

MATERIALS AND METHODS

All thirty one cases of non Hodgkin's lymphoma arising in the nose(12), maxillary sinus(1), tonsil(13) and nasopharynx(5) were selected from the surgical pathology files of the Kyung Hee Medical Center. Tissues from each case were fixed in formalin and embedded in paraffin. A tumor was considered to have arisen in either the sinonasal tract or Waldeyer s ring if the lymphoma was extensively involved the upper aerodigestive tract and was accompanied by local symptoms at the initial presentation. An attempt to review the clinical records and to obtain follow up information was made in all cases. When possible, the clinical stage was obtained. The patients were staged according to the Ann Arbor system. All lymphomas were histologically classified according to the Working Formulation. The histologic findings of lethal midline granuloma summarized as an angiocentric pattern, were also evaluated. Follow up ranged from two months to 7 years with a median of 3 years. Patient survival was evaluated by the Log Rank test using the NCSS (Number Cruncher Statistical System) program.

All cases were immunophenotyped using avidin biotin peroxidase complex method on the paraffin embedded sections. Briefly 5-μ sections were mounted on poly L-lysine coated slides, deparaffinized and incubated with hydrogen peroxide. Sections were incubated for 1 hour with primary antibody, followed by the addition of biotinylated horse antimouse immunoglobulin (Vector ABC kit) and the avidin biotin complex for 30minutes each. The slides were then stained with 5' diaminobenzidine tetrahydrochloride and counter-stained with Mayer's hematoxylin. The monoclonal antibodies used in this study and their commercial sources are the following : leukocyte common antigen (CD45RB : Dako, diluted 1 : 50). L26 (CD20, Dako, diluted 1 : 50), UCHL-1 (CD45RO. Dako, diluted 1 : 50) and CD68 (Dako, diluted 1 : 50). Selected cases were also stained with antibodies CD43 (Dako, diluted 1 : 25), MT1 (Biotest, diluted 1 : 40) and MB2 (Biotest, diluted 1 : 40) against T-and B-cell antigen respectively.

The EBV RNA in situ hybridization studies were performed using a fluorescein conjugated EBV oligonucleotides probe (Dako) complementary to the two encoded small non polyadenylated RNAs (EBER-1 and EBER-2). The EBERs are the most heavily transcribed up to 10^7 copies per cell in latently infected cells (Glickman et al., 1988). Most EBERs localize to the cell nucleus where they are complexed with cellular La protein. The procedure used for the in situ hybridization studies has been described. Briefly, formalin fixed paraffin embedded tissue sections were placed on poly L-lysine coated slides, baked at 37℃, deparaffinized, incubated in ethanol and air dried. Sections were digested for 30 minutes with protenase K, acetylated with acetic anhydride and triethanolamine, dehydrated and air dried. The sections were hybridized overnight at 42℃ with a fluorescein conjugated probes. After washing in 0.1% triton X-100, detection was performed with alkaline phosphatase conjugated rabbit anti-FITC followed by development with 5-bromo-4-chloro-3-indolylphosphate (BCIP) and nitroblue tetrazolium (NBT). A black or dark blue color within the nucleus was considered as a positive reaction. A known EBV positive Hodgkin's disease served as a positive control in each run. Any slide negative for EBER and all non neoplastic lesions were used for a negative internal control.

RESULTS

The clinical and histologic findings and the results of immunophenotyping and in situ hybridization stu-

Table 1. Summary of SinoNasal Lymphomas

Case	Age	Sex	Site	Stage	Histology	Phenotype	EBER	Follow-Up
1	50	M	NOSE	II E	DM+AC	T	+	LOST, 2M
2	30	F	NOSE	I E	DL+AC	T	+	DIED, 6M
3	50	M	NOSE	I E	DM+AC	T	+	DIED, 9M
4	30	M	NOSE	I E	DL+AC	T	+	ALIVE, 5Y5M
5	73	F	NOSE	I E	DL+AC	T	+	DIED, ?
6	63	M	NOSE	I E	DL+AC	T	+	ALIVE, 2Y3M
7	71	M	NOSE	I E	DL	B	−	ALIVE, 7M
8	62	F	NOSE	I E	DL+AC	T	+	DIED, 2M
9	49	M	NOSE	I E	IBS	T	+	DIED, 2Y
10	32	M	NOSE	II E	DL+AC	T	+	ALIVE, 3Y
11	26	F	NOSE	I E	DL+AC	T	+	ALIVE, 6Y
12	58	M	NOSE	I E	DL	T	+	ALIVE, 7Y
13	77	M	MAXILLA	I E	DL+AC	T	+	ALIVE, 1Y

DL : Diffuse large cell lymphoma.
DM : Diffuse mixed small and large cell lymphoma.
IBS : Large cell immunoblastic lymphoma.
AC : Angiocentric and angiodestructive pattern.
EBER : Epstein Barr virus Encoded RNA *In situ* hybridization.

Table 2. Summary of Waldeyer's Ring Lymphomas

Case	Age	Sex	Site	Stage	Histology	Phenotype	EBER	Follow-Up
1	57	M	TONSIL	II	DL	B	−	ALIVE, 2Y
2	26	F	TONSIL	III	FL	B	−	DIED, 2Y8M
3	36	F	TONSIL	I	FL	B	−	ALIVE, 5Y
4	42	F	TONSIL	I	IBS	B	−	ALIVE, 1Y
5	17	M	TONSIL	I	DL+AC	T	+	DIED, 5M
6	6	M	TONSIL	I	DL	B	−	ALIVE, 5Y
7	39	M	TONSIL	I	DL	B	−	DIED, 6M
8	51	F	TONSIL	I	DL	B	−	DIED, 1Y
9	57	F	TONSIL	I	DL	B	−	NA
10	35	F	TONSIL	I	FL	B	−	ALIVE, 6Y
11	68	M	TONSIL	I	DL	B	−	DIED, 7Y*
12	46	M	TONSIL	I	DL	B	−**	ALIVE, 7Y
13	52	M	TONSIL	I	LP	B, LAMBDA	+	ALIVE, 3Y
14	42	M	NASOPHARYX	II	IBS	T	+	LOST, 4M
15	66	F	NASOPHARYX	II	IBS	B	−	ALIVE, 7Y
16	42	M	NASOPHARYX	I	DL	B	+	ALIVE, 5Y5M
17	67	M	NASOPHARYX	II	DL	B	−	ALIVE, 1Y7M
18	62	M	NASOPHARYX	II	DL+FL	B	−	ALIVE, 2Y

* stomach lymphoma subsequently developed after 7yrs.
** EBER positivity was present on the surface epithelium.
DL : Diffuse large cell lymphoma.
LP : Lymphoplasmacytic lymphoma.
IBS : Large cell immunoblastic lymphoma.
AC : Angiocentric and angiodestructive pattern.
FL+DL : follicular and diffuse large cell lymphoma.
NA : Not available.
EBER : Epstein Barr virus Encoded RNA *In situ* hybridization.

dies for 13 patients with sinonasal lymphoma and 18 patients with Waldeyer's ring lymphoma are summarized in table 1 and table 2 respectively. Patients with sinonasal lymphomas had a median age of 50 years (range 26-77) with a 9 : 4 male to female ratio. The patients with Waldeyer's ring lymphomas had a median age of 42 years (range 6-68) with an 11 : 7 male to female ratio. Eleven sinonasal lymphomas were in stage Ⅰ and two in stage Ⅱ. Twelve Waldeyer ring lymphomas were in stage Ⅰ, five in stage Ⅱ. and one in stage Ⅲ.

Histology

The sionasal lymphomas were morphologically classified as follows : 10 diffuse large cell lymphoma ; 2 diffuse mixed small and large cell lymphoma and 1 diffuse large cell immunoblastic lymphoma. The Waldeyer's ring lymphomas included the following : 10 diffuse large cell lymphomas, 3 diffuse large cell immunoblastic lymphomas, 3 follicular large cell lymphomas, 1 follicular and diffuse large cell lymphoma and 1 small lymphocytic lymphoma with plasmacytic differentiation. Histologic features of angiocentricity, angioinvasion, necrosis and inflammatory cell reaction were found in 11 of 13 sinonasal lymphomas (Fig. 1) and one of the 18 Waldeyer's ring lymphomas.

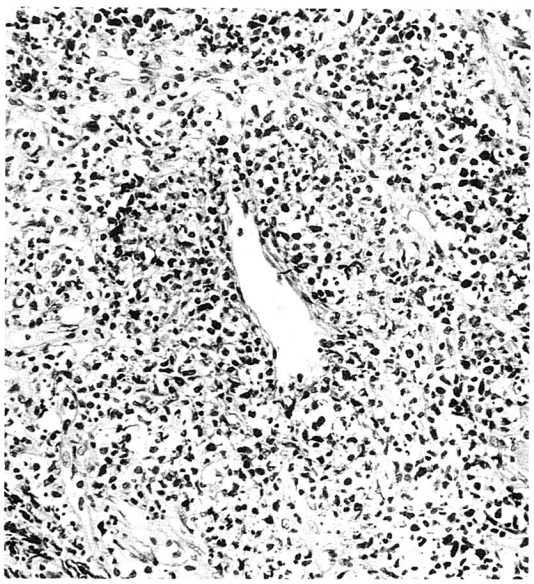

Fig. 1. Nasal T-cell lymphoma with an angiocentric pattern and an admixture of inflammatory cells.

Immunophenotype

Immunophenotypic analysis of sinonasal lymphomas revealed 11 T cell and 1 B cell neoplasm. Most Waldeyer's ring lymphoma were B cell neoplasms. On small lymphocytic lymphoma with plasmacytic differentiation shows a lambda light chain restriction in the cytoplasm. Two Waldeyer's ring lymphomas showed T cell lineage with angiocentric pattern in one of them. The cases interpreted as B cell were all CD20 (L26) positive and negative for CD45RO, CD43 and MT-1. The cases interpreted as T cell were all CD20 negative and positive for CD45RO, CD43 or MT1.

EBER in situ hybridization

Many EBER positive cells (Fig. 2) were found in 12 out of the 13 cases of sinonasal lymphomas all with T cell immunophenotype and angiocentric pattern. One case of B cell sinonasal lymphoma was EBER negative. The EBER positive cells were found in 4 out of the 18 cases of Waldeyer's ring lymphoma. Two T cell lymphomas, especially with angiocentric patterns had many EBER positive cells. One case of B cell lymphoma (Case 13) demonstrated several

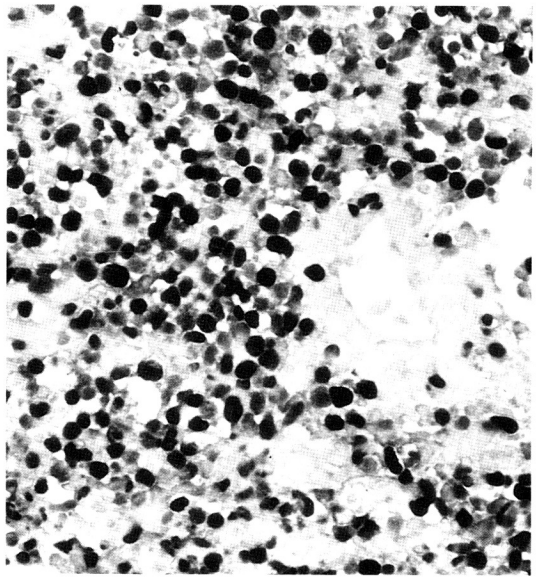

Fig. 2. In situ hybridization for Epstein-Barr virus RNA in a T-cell lymphoma showing diffuse nuclear staining of the tumor cells.

distinct EBER positivities in the two repeat biopsy specimens of the same site, the tonsil. The other B cell lymphoma (Case 16) showed a few (< 10/medium powered field X 200) EBER positive cells. One case (Case 12) showed a few distinct EBER positive cells on the normal surface epithelium. EBER positive cells were histologically found in 11 of 20 diffuse large cell lymphoma, 2 diffuse mixed small and large cell lymphoma, 2 of 4 immunoblastic lymphoma and 1 small lymphocytic lymphoma with plasmacytic differenitation. Four follicular large cell lymphomas were EBER negative.

Survival analysis

Survival was statistically analyzed depending on the presence of EBER, immunophenotypes and location of the tumor by the Log-Rank test. There was no significant difference in survival between EBER positive and negative lymphomas (probability =0.46). The comparison between Waldeyer's ring and Sinonasal lymphoma (probability=0.58) did not reveal any significant difference. However, survival with reference to the cell type B or T revealed no significant difference either (probability=0.20) ; the immunophenotype of the lymphomas was more closely related to survival rather than presence of EBER or the location of the tumor.

DISCUSSION

Primary malignant lymphomas of the upper aerodigestive tract, including those of Waldeyer's ring, the nasal cavity and paranasal sinuses, are an important and interesting group of neoplasm because of their frequent extranodal presentation and there is much controversy concerning their nature and behavior. The incidence of nasal/nasopharyngeal lymphomas in Western populations was 1.5%-3% (Frierson et al., 1989), whereas they were 7-8% of all non-Hodgkin's lymphomas in the Oriental population (Ho et al., 1984 ; Ng et al., 1986 ; Maeda et al., 1988) and in Peru (Arber et al., 1993). In Korea, the incidence was 6.2% (Kim et al., 1992). Diverse terminology has been applied to this group of nasal lymphomas presenting as a mass or destructive, ulcerative necrotizing lesion in the midline structures. The terms, lethal midline granuloma, malignant midline granuloma, polymorphic reticulosis, malignant midline reticulosis and angiocentric immunoproliferative lesion were used. The term angiocentric immunoproliferative lesion encompasses a spectrum of post-thymic T cell proliferation occuring in a variety of extranodal sites (Lipford et al., 1988). Immunophenotypically, geographic difference has been reported : studies of (Yamanaka et al., 1985 ; Chan et al., 1987) the Oriental population including our studies show a striking predominance of T cell tumors in nasal lymphomas. This T cell predominance differs from the immunophenotype of other head and neck lymphomas, especially Waldeyer's ring lymphoma, which are predominantly of B cell neoplasms. However, most studies of sinonasal lymphomas in the United States (Frierson et al., 1989) and Germany (Fellbaum, 1989) demonstrate them to be predominantly of B cell lineage. In our study, most sinonasal lymphomas showed T cell lineage, and showed angiocentric pattern with necrosis in 10 of 13 cases. In comparison with the sinonasal lymphomas, the tonsillar and nasopharyngeal lymphomas revealed B cell lineage except in 2 cases. Unlike T cell lymphomas of the lymph nodes, T cell receptor gene rearrangement is rarely demonstrated in T cell lymphomas of nose/nasopharynx. Ho et al.(1990) reported gamma chain gene rearrangement only in one of 8 cases. Several studies of nasal/nasopharyngeal lymphomas have failed to find evidence of clonal rearrangements for the beta chain of the T cell receptor (Weiss et al., 1988 ; Medeiros et al., 1991). Interestingly the majority of cases expressed cell surface antigens associated with natural killer cell differentiation in the T cell lymphoma with a predilection site of sinonasal lymphomas (Ng et al., 1987 ; Kanavaros et al., 1993). It was not clear whether most nasal lymphomas were possibly derived from T lymphocytes.

Recently Harabuchi et al.(1990) reported EBV-DNA in 5 cases of nasal T cell lymphomas presenting clinically as lethal midline granuloma. Ho et al.(1990) reported the EBV genome in 10 of 11 nasal lymphomas occuring in Chinese patients. Despite the B cell predominance in Western literature, EBV has been associated with B cell and T cell sinonasal lymphomas (Weiss et al., 1992). A stong association has been shown between nasal/nasopharyngeal T cell lymphoma and EBV, mostly in Asian and Peruvian patients (Arber et al., 1993) and more recently in a French series of lethal midline granuloma(Kanavaros et al., 1993). The association is much weaker for B cell lymphomas. On the other hand, for Waldeyer's ring lymphomas, association with EBV is very rare. In our study, EBV

Table 3. Summary of EBV and lymphomas of the upper aerodigestive tract in the literature

Study		Population	Sinonasal lymphoma		Waldeyer's ring lymphomas		EBV
			T cell	B cell	T cell	B cell	
Harabuchi	1990	Japanese	5/5				S : DNA
Ho	1990	Honkong	8/8	2/3			S : DNA
Weiss	1992	American	3/3	2/5		2/10	I : DNA
Arber	1993	Peruvians	11/11	1/2			I : EBER
Kanavaros	1993	French	7/7				I : EBER, DNA
Korbjuhn	1993	German	3/6				I : EBER
Medeiros	1992	American	3/3				I : EBER
Borisch	1993	Swiss	5/6			0/1	I : EBER
Present	1993	Korean	12/12	0/1	2/2	2/16	I : EBER

encoded RNA using in situ hybridization, was positive in 92%(12/13) of sinonasal and 22%(4/18) of Waldeyer's ring lymphomas. All cases of T cell lymphomas occuring in Waldeyer's ring and sinonasal areas expressed EBER positivity. However, EBER was positive in 12.5%(2/16) of B cell Waldeyer's ring lymphomas. Our findings are similar to the prevalence of EBV positive T cell lymphomas in the literature(Table 3). We also analyzed angiocentric pattern according to EBER positivity. Angiocentric patterns with extensive necrosis and a mixture of inflammatory cells were present in 10 cases of sinonasal lymphoma with T cell lineage and one case of Waldeyer's ring lymphoma with T cell lineage. EBER positivity was found in all eleven cases of lymphomas with angiocentric pattern. Dual parameter analysis confirmed that EBERs were localized to T lineage cells (CD43-positive, CD20-negative) in angiocentric immunoproliferative lesion(Medeiros et al., 1992). However, 5 cases of lymphomas without angiocentric pattern showed EBER positive and histologically included one case of lymphoplasmacytic lymphoma, 2 cases of diffuse large cell lymphomas and 2 cases of large cell immunoblastic lymphoma. It was interesting that the low grade lymphoma, lymphoplasmacytic type was positive for EBER in our study (Case 13). Among B cell lymphomas, Burkitt's lymphoma and lymphoproliferative disorder occuring in immunocompromised patients has described EBV positive. The evidence of EBV was not present in the follicular lymphomas and low grade lymphomas including monocytoid lymphoma (Chang, 1993). In the extremely rare case of small lymphocytic lymphoma with Reed Sternberg-like cells, EBV has been demonstrated (Momose et al., 1992). Although double labelling immunohistochemistry/in situ hybridization was not performed in our study, EBER was present in both B and T cell sinonasal non Hodgkin's lymphomas and Waldeyer's ring lymphomas. However EBER was more strongly associated with the T cell lymphomas, angiocentric pattern and sinonasal location rather than with the B cell lymphomas and Waldeyer's ring location. All these findings suggest that EBV may play an etiologic role and is not simply a passenger virus or merely a site mediated phenomenon for T cell lymphomas of the sinonasal location. By southern blotting, the EBV was found to be present in a monoclonal population (Ho et al., 1990). The mechanism by which EBV can enter into tumor cells of T cell lymphomas, is not clear. Known targets for EBV infection include B lymphocytes and epithelial cells of the nasopharynx. However, it has also been shown that human thymocytes(Watry et al., 1991) and cytotoxic/suppressor T lymphocytes express the cell surface receptor for EBV (CD21) (Sauvageau et al., 1990). EBV receptor expression on the T cells was about 10 and 51 times less than that on Molt-4 and Raji cells respectively. Indeed, the CR2 (CD21) EBV receptor was expressed in about 30% of human peripheral blood T lymphocytes (Fischer, 1991) and was detected on tumor cells in 1 of 7 nasal T cell lymphomas (Kanavaros et al., 1993). Thus, it is possible that in most EBV positive T cell lymphoma, the EBV infection has occured during transient CD21 expression before clonal expansion of the transformed cells. Alternatively molecules other than CD21 may also play the role of EBV receptor on T cells. Two common biotypes of EBV, A and B or 1 and 2, have been described that differ at the EBNA -2, -3, -4 and -6 gene loci. Borisch et al.(1993) reported increased frequency of

type B EBV in malignant lymphoma of anigocentric type and indicated the association of EBV with non Hodgkin's lymphoma may depend on tumor type rather than on its location. The occurrence of the rare subtype 2 may relate to a covert immune defect. In lymphoma patients with immunodeficiency, acquired or iatrogenic, subtype 2 is found in approximately half of cases. We also questioned the significance of EBV infection in these lymphomas. The patients of peripheral T cell lymphomas containing EBV DNA had an aggressive clinical course and poor response to chemotherapy (Su et al., 1991). EBV associated T cell lymphoma should be treated as a separate disease entity. However, our patient survival did not reveal any significant difference between EBER positive and negative lymphomas (probability=0.46). Studies will be needed to clarify the clinical or prognostic significance of EBV infection in lymphomas. In summary, there was a possible relationship between the location and immunophenotypes of the tumor and the presence of EBER, however the survival was not significantly affected by these factors in our study.

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